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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/457,926	12/08/1999	BURTON G. CHRISTENSEN	P-061-R2	8221

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EXAMINER
BAKER, MAURIE GARCIA

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 07/02/2002 25

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/457,926	Christensen et al
Examiner	**Art Unit**
Maurie Garcia Baker, Ph. D.	1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 11, 2002*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *41-46, 49-51, 53-55, 57, and 58* is/are pending in the applica

4a) Of the above, claim(s) *42, 44-46, 57, and 58* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *41, 43, 49-51, and 53-55* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The Response filed via fax on April 11, 2002 (Paper No. 24) is acknowledged. Claims 50 and 51 were amended and no claims were cancelled or added. Therefore, claims 41-46, 49-51, 53-55, 57 and 58 are pending.

2. Claims 42, 44-46, 57 and 58 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species, there being no allowable generic claim. Applicant is reminded that **only** upon the allowance of a generic claim are they entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. See previous action for discussion of non-elected species claims.

3. Therefore, claims 41, 43, 49-51 and 53-55 are examined on the merits in this action.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said

subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 41, 43, 49-51 and 53-55 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Truett (US 5,693,791; on PTO-1449) in view of Boeckh et al (Antimicrob. Agents Chemother., 1988, Vol. 32, No. 1, pp. 92-95; of record) and Renoud-Grappin et al (Antiviral Chem. and Chemotherapy, Vol. 9, No.3, 1998, pp. 205-223) and Staroske et al (Tet. Lett., 1998, Vol. 39; on PTO-1449).

Truett teaches the "linking of diverse antibiotic moieties via difunctional organic compounds" (see column 1, lines 8-9). Specifically, dimers are taught having the structure A-L-B, where A and B are various antibiotic moieties (see "Summary", columns 1-6, especially column 1, lines 46-64). A variety of linkers and linkage chemistries are taught (see columns 25-32). The reference teaches that the linkage of two antibiotic moieties can create compounds of new activity

(see column 1, lines 1-30) and that "two antibiotic moieties can be linked in which one is known to attack Gram positive bacteria and another to attack Gram negative bacteria" (see column1, lines 27-30). Truett teaches a dimeric compound where one of the antibiotic moieties is ceftazidime (see column 3, line 7). Ceftazidime is a beta lactam antibiotic that reads on the elected species that is set forth in claim 53, see structure in the instant Figure 6B-2. Truett lacks the teaching of linking vancomycin with ceftazidime.

However, it was well known in the art at the time of filing to use combination therapy with vancomycin and ceftazidime. For example, Boeckh et al teach that this combination therapy is used to "cover a broad spectrum of gram positive and gram negative bacteria" (see page 92, 1st paragraph). The reference teaches the pharmacokinetics of the combination of vancomycin and ceftazidime, administered to humans (see Abstract and Table 1), thus pharmaceutical compositions of the drugs are well known.

Renoud-Grappin et al teach that one way to achieve effective combination therapy is to covalently link two different drugs. See page 208, first column, first full paragraph of the reference, which describes using heterodimers for combination therapy linked "through an appropriate spacer, in an attempt to combine the inhibitory capacity" of two different classes of molecules. The reference also describes that one would attempt such an approach to span two binding sites on the target. Renoud-Grappin et al also discuss combining different drugs to "prevent the emergence of drug-resistant virus strains" and set forth three

main reasons for combination therapy (see page 207, 2nd column, 2nd paragraph). It is recognized that the linked compounds of Renoud-Grappin et al (see, for example, Figure 4 of the reference) are anti-virals and not antibiotics; however, it is the examiner's position that one of ordinary skill would recognize the relevance of preventing the emergence of drug-resistant strains for both classes of molecules since such was well established in the art.

Additionally, vancomycin dimers were also known in the art at the time of filing. Staroske et al discuss both "head-to-head" and head-to-tail" dimers (see Figure 3) and that in "light of recent reports of vancomycin -resistant bacteria" there is a "strong incentive for the development of more potent antibiotics" (page 4917, bottom). The reference also teaches that dimeric vancomycin compounds exhibit improved antibacterial activity, see for example, page 4918, top. Specifically, the dimers of Staroske et al are linked from the amino terminus of one vancomycin moiety to the carboxy terminus of another (see Scheme 1, page 4919). The reference also contemplates linking of the vancomycin at the vancosamine moiety (see page 4920, last two paragraphs).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to link vancomycin and ceftazidime, based on the teaching of Truett concerning the linking of diverse antibiotic moieties combined with the teaching of Boeckh et al to perform combination therapy using the drugs, the teaching of Renoud-Grappin concerning linking drugs to perform combination therapy and the teaching of Staroske et al concerning vancomycin

dimers linked through the amino and carboxy terminus. Specifically, Truett teaches that two antibiotics, one known to attack Gram positive bacteria and another to attack Gram negative bacteria can be linked and the advantages of doing such, and Boeckh et al teach that vancomycin and ceftazidime fulfill these requirements. Renoud-Grappin teach that one way to achieve effective combination therapy is to covalently link two different drugs. Finally, Staroske et al teach that vancomycin can be linked at specific linkage sites. One of ordinary skill would have been motivated to covalently link vancomycin with ceftazidime to create a broad spectrum antibiotic compound to fight antibiotic resistant strains. One of ordinary skill would also have had a reasonable expectation of success based on the fact that Staroske et al teaches linking chemistry for vancomycin.

Response to Arguments

7. Applicant's arguments filed April 11, 2002 have been fully considered but were not found persuasive. The examiner's rationale is set forth below.

8. Applicant argues that there is insufficient motivation and no reasonable expectation of success. However, the examiner maintains that one of ordinary skill in the art at the time of filing would have been motivated and had a reasonable expectation of success for the reasons set forth in the rejection and the further reasons below.

9. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

10. Also, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Also, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

11. In this case, the examiner maintains that the *combined* teachings of the cited references render the claimed invention obvious. The teachings referred to in the rejection above are strong motivation. Also, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent,

that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the beneficial result of the combination of references is creating a broad spectrum antibiotic compound to fight antibiotic resistant strains.

12. Applicant argues that because the heterodimer approach taught by the Renoud-Grappin reference did not work, that this is a teaching away from the instant invention (Response, page 6 bottom – page 7). See MPEP 2143.01: The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991).

13. Thus, the examiner's position is that although the teachings of the Renoud-Grappin reference may "conflict" with respect to the failure of the heterodimeric approach to achieve effective combination therapy, the reference *suggests solutions*: "chemists should explore other linkers and attachment sites for these linkers" (Renoud-Grappin, page 219, 2nd column, last paragraph). Also, although a prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; "the nature of the teaching is highly relevant and must be

weighed in substance" (see MPEP 2145). The examiner maintains that the teachings of the Renoud-Grappin reference still render the claimed invention obvious when considered *as a whole* and in the context of the rest of the prior art cited.

14. Note that "[o]bviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart,* 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). No ***evidence*** has been provided in support of applicant's conclusion (see also paragraph 15 below) that there is no reasonable expectation of success based on the teachings of the Renoud-Grappin reference (Response, page 9, bottom). The examiner maintains that although the compounds of Renoud-Grappin did not show an increase in inhibitory activity, the reference suggests solutions (see paragraph 13 above) and maintains that the *combined* teachings of the references would have suggested the claimed invention to one of ordinary skill in the art.

15. Applicant's arguments do not rise to the level of factual evidence. See MPEP § 716.01(c): The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Also, it appears that applicant is arguing that their claimed dimeric antibiotic compounds have some sort of superior activity (see for example, Response, page 7, middle); however, objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results... See, for example, *In re*

De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence"). Lastly, any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (In MPEP § 716.02).

16. Lastly, in response to applicants argument that the rejection represents only an "obvious to try" rationale, the following from MPEP 2145 is noted:

> The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. . . . In others, what was obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.). See the cases cited in O 'Farrell for examples of decisions where the court discussed an improper "obvious to try" approach. See also In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) and In re Ball Corp., 925 F.2d 1480, 18 USPQ2d 1491 (Fed. Cir. 1991) (unpublished) for examples of cases where appellants argued that an improper "obvious to try" standard was applied, but the court found that there was proper motivation to modify the references.

17. The examiner's position is that the references ***do*** indicate which parameters are critical and ***do*** provide direction as to which of many possible choices is likely to be

successful. For example, Boeckh et al specifically teach combination therapy with vancomycin and ceftazidime and that this combination therapy is used to "cover a broad spectrum of gram positive and gram negative bacteria", Truett teaches the "linking of diverse antibiotic moieties via difunctional organic compounds" and Renoud-Grappin teaches the heterodimeric approach for combination therapy, and improvements thereon by exploration of "other linkers and attachment sites for these linkers".

18. Thus for these reasons, the rejection of claims 41, 43, 49-51 and 53-55 under 35 U.S.C. 103(a) is maintained.

Status of Claims/ Conclusion

19. No claims are allowed.

20. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no

event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

22. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PADMASHRI PONNALURI
PRIMARY EXAMINER

Maurie Garcia Baker, Ph.D.
June 28, 2002